Novel Approaches to Future Therapy of Hepatitis B

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Hepatitis B is one of the most prevalent viral diseases in the world. It leads to chronic liver disease in 10% of infected individuals, putting them at an increased risk for liver-related morbidity and mortality from complications of cirrhosis and hepatocellular carcinoma. Despite the success of universal hepatitis B vaccination in many countries, this disease remains a major public health problem, resulting in more than 500,000 deaths per year. Although the current therapy for chronic hepatitis B (CHB) is effective, it is not optimal; novel approaches to the management of CHB are needed. The currently available therapies are either interferon-a based or nucleoside analogues. The nucleoside analogues, however, target a narrowly focused step of viral infection—the DNA synthesis step.[1] Although several nucleoside analogues have been developed with different resistant profiles to address the drug resistance issue, the overall efficacy is still questionable.[1] Drugs have been developed to target other steps of HBV infection, such as viral entry, encapsidation, assembly, and viral secretion.[2-5] In addition, nucleic acid technology, such as antisense, ribozyme, and siRNA,[6-8] has been applied to inhibit HBV replication *in vitro* and *in vivo*. Immunotherapy, based on novel antiviral cytokines and activation of virus-specific immunity,[9,10] holds promise as an alternative therapeutic approach. An improved understanding of virus-host interactions, advances in gene therapy, the development of molecular therapies targeted at different stages of the hepatitis B virus life cycle, and new insight into various approaches of immune modulation will lead to the development of better therapeutic agents for the management of CHB.[1] These advances herald a new era of combination therapy.

References

1. Loomba R, Liang TJ. Novel approaches to new therapies for hepatitis B virus infection. *Antivir Ther* 2006;11:1-15.
2. Deres K, Schroder CH, Paessens A, Goldmann S, Hacker HJ, Weber O, Kramer T, et al. Inhibition of hepatitis B virus replication by drug-induced depletion of nucleocapsids. *Science* 2003;299:893-896.
3. King RW, Ladner SK, Miller TJ, Zaifert K, Perni RB, Conway SC, Otto MJ. Inhibition of human hepatitis B virus replication by AT-61, a phenylpropenamide derivative, alone and in combination with (-)beta-L-2',3'-dideoxy-3'-thiacytidine. *Antimicrob Agents Chemother* 1998;42:3179-3186.
4. Block TM, Lu X, Mehta AS, Blumberg BS, Tennant B, Ebling M, Korba B, et al. Treatment of chronic hepadnavirus infection in a woodchuck animal model with an inhibitor of protein folding and trafficking. *Nat Med* 1998;4:610-614.
5. Dyson MR, Murray K. Selection of peptide inhibitors of interactions involved in complex protein assemblies: association of the core and surface antigens of hepatitis B virus. *Proc Natl Acad Sci USA* 1995;92:2194-2198.
6. Brown-Augsburger P, Yue XM, Lockridge JA, McSwiggen JA, Kamboj D, Hillgren KM. Development and validation of a sensitive, specific, and rapid hybridization-ELISA

assay for determination of concentrations of a ribozyme in biological matrices. *J Pharm Biomed Anal* 2004;34:129-139.
7. McCaffrey AP, Nakai H, Pandey K, Huang Z, Salazar FH, Xu H, Wieland SF, et al. Inhibition of hepatitis B virus in mice by RNA interference. *Nat Biotechnol* 2003;21:639-644.
8. Morrissey DV, Lockridge JA, Shaw L, Blanchard K, Jensen K, Breen W, Hartsough K, et al. Potent and persistent in vivo anti-HBV activity of chemically modified siRNAs. *Nat Biotechnol* 2005;23:1002-1007.
9. Horiike N, Fazle Akbar SM, Michitaka K, Joukou K, Yamamoto K, Kojima N, Hiasa Y, et al. In vivo immunization by vaccine therapy following virus suppression by lamivudine: a novel approach for treating patients with chronic hepatitis B. *J Clin Virol* 2005;32:156-161.
10. Heathcote J, McHutchison J, Lee S, Tong M, Benner K, Minuk G, Wright T, et al. A pilot study of the CY-1899 T-cell vaccine in subjects chronically infected with hepatitis B virus. The CY1899 T Cell Vaccine Study Group. *Hepatology* 1999;30:531-536.